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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/834,926	04/16/2001	Peter Pochlauer	2001_0331A	5439

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[REDACTED] EXAMINER

ZUCKER, PAUL A

ART UNIT	PAPER NUMBER
1621	8

DATE MAILED: 08/08/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)
	09/834,926	POCHLAUER ET AL.
	Examiner	Art Unit
	Paul A. Zucker	1621

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 29 April 2002 and 28 May 2002.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 11-14 and 16-23 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 11-14 and 16-23 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) The proposed drawing correction filed on _____ is: a) approved b) disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
- 1.) Certified copies of the priority documents have been received.
- 2.) Certified copies of the priority documents have been received in Application No. _____.
- 3.) Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
a) The translation of the foreign language provisional application has been received.
- 15) Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- | | |
|--|--|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s). _____ . |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ . | 6) <input type="checkbox"/> Other: _____ . |

DETAILED ACTION

Current Status

1. This action is responsive to Applicant's amendment of 29 April 2002 in Paper No 6 and Supplemental amendment of 28 May 2002 in Paper No 7.
2. Receipt and entry of Applicant's amendments is acknowledged.
3. Applicants' cancellation of claim 15 is acknowledged.
4. Applicants' addition of new claims 20-23 is acknowledged.
5. Claims 11-14 and 16-23 are outstanding.
6. The rejection under 35 USC § 112, second paragraph, set forth in paragraph 6 of the previous Office Action in Paper No 5 is withdrawn in response to Applicant's amendment.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 11-14, 16-21 and 23 are finally rejected under 35 U.S.C. 103(a) as being unpatentable over Effenberger et al (US 4,859,784 08-1989) and further in view of Collet et al (Bulletin de la Société Chimique de France 1973, 12, Pt. 2, pages 3330-

3334) and further in view of McMasters (Chem2O06 Laboratory 1997, Expt. 1, Part

B. Recrystallization and Melting Point Determinations. from world wide web

:chemistry.mcmaster.ca/~chem2o6/labmanual/microscale/ms-recrs.html).

Instantly claimed is a process for the purification of (R) and (S)- α -hydroxycarboxylic acids which consists essentially of recrystallizing impure acids in a hydrocarbon solvent optionally in the presence of a co-solvent. The source of the hydroxycarboxylic acid, as claimed, is an enzyme-catalyzed addition of cyanide ion.

Effenberger teaches (Column 1, line 66- Column 3, line 11) a method for the synthesis of optically active cyanohydrins via the reaction of an aromatic aldehyde with hydrocyanic acid in the presence of the enzyme D-oxynitrilase as a catalyst.

Aromatic hydrocarbons (Column 2, lines 52-56) are taught as solvent and the presaturation with water or an aqueous buffer corresponding to the instant co-solvent is also taught (Column 2, line 66- column 3, line 7). Effenberger further teaches (Column 2, lines 52-65) the use of t-butyl methyl ether as a reaction solvent.

The amount of water in the water-saturated aromatic solvent is considered to fall within the limits of instant claim 19. Effenberger specifically teaches (Column 2, line 16) the use of o-chlorobenzaldehyde in the process. This corresponds to the intermediate required for synthesis of 2-chloromandelic acid (cf. instant claim 14).

Effenberger exemplifies (Column 3, line 49 – column 4, line 54) the cases of benzaldehyde, o- and m-methoxybenzaldehyde which proceed with diastereomeric excesses of 99.3, 90 and 98%, respectively, for the crude product cyanohydrins.

Effenberger is silent with regard to the process for conversion of the product cyanohydrins into optically active 2-hydroxycarboxylic acids but does specifically suggest (Column 3, lines 15-19) that the crude solutions of cyanohydrins can be directly converted into optically active 2-hydroxycarboxylic acids:

“It is not necessary that the crude solutions be purified or treated any further, but can be directly used in further processes under certain conditions, for instance by hydrolysis into the corresponding optically active 2-hydroxycarboxylic acids.”

Effenberger is also silent with regard to the recrystallization from an aromatic hydrocarbon solvent, with optional co-solvent, to increase chemical and optical purity.

Collet, however, teaches (page 3332, right column, last paragraph) a process for the synthesis of optically pure substituted mandelic acids via the acidic hydrolysis of racemic halomandelonitriles at room temperature with stirring for 15 hours followed by extraction from the hydrolysis mixture at room temperature. Collet further teaches (Page 3333, left column, 2nd and 3rd paragraphs from bottom under heading “Acides (+) and (-) o-chloromandéliques”) resolution of the racemic o-chloromandelic acids via formation of the diastereomeric salts with (-)-ephedrine, recovery of the free acids from their salts to give optically enriched (R)-o-chloromandelic acids which can then be rendered optically pure by repeated recrystallization from benzene.

Collet is silent with regard to the use of an optional cosolvent as is instantly claimed.

McMasters, however, teaches (Page 1, first full paragraph) a conventional recrystallization process. McMasters further teaches (Page 2, 2nd and 3rd full paragraphs) the use of a miscible organic co-solvent and the method of choosing a solvent mixture. This teaching along with Effenberger's teaching of the suitability for use as a reaction solvent of t-butyl methyl ether would lead one of ordinary skill in the art to consider the selection of t-butyl methyl ether as a co-solvent in the process of Collet.

It would naturally occur to one of ordinary skill in the art to combine the method for the production of optically active mandelonitriles taught by Effenberger with Collet's process of hydrolysis of mandelonitriles to generate the corresponding mandelic acids (2-hydroxycarboxylic acids). Such a combination results in nearly optically pure mandelic acids after extraction of the hydrolysis mixture. Effenberger in fact suggests a combination of such processes. It is also obvious to use recrystallization from benzene as disclosed by Collet to give optically pure (R)-2-chloromandelic acid from the optically enriched material.

Thus the instantly claimed process would have been obvious to one of ordinary skill in the art. The motivation would have been to use the method of Effenberger and Collet to produce optically pure 2-hydroxycarboxylic acids which are important as pharmaceuticals and as intermediates for the synthesis of pharmaceuticals.

McMasters provides the teaching required to modify the process of Collett. Since all

references are drawn to the production of the same ultimate products and specifically teach the necessary elements the expectation for success would be extraordinarily high.

8. Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Effenberger et al (US 4,859,784 08-1989) and Collet et al (Bulletin de la Société Chimique de France 1973, 12, Pt. 2, pages 3330-3334) and McMasters as applied to claims 11-14, 16-21 and 23 above, and further in view of Bryker et al (US 4,983,771 01-1991).

Instantly claimed is a process for the purification of (R) and (S) - α -hydroxycarboxylic acids which consists essentially of recrystallizing impure acids in a hydrocarbon solvent in the presence of the co-solvent methyl isobutyl ketone. The source of the hydroxycarboxylic acid, as claimed, is an enzyme-catalyzed addition of cyanide ion.

Effenberger, Collet and McMasters are all silent with regard to the use of methylisobutyl ketone (MIBK) as a solvent for mandelic acids.

Bryker, however, teaches (Column 5, lines 14-58) the use of methyl isobutyl ketone in the recovery and isolation of mandelic acid used in the resolution of D,L - α -phenethylamine. This teaching along with McMasters' teaching of the crystallization process would lead one of ordinary skill in the art to consider the selection of t-butyl methyl ether as a co-solvent in the process of Collet.

Thus the instantly claimed process would have been obvious to one of ordinary skill in the art. The motivation would have been to use the method of Effenberger and

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Collet to produce optically pure 2-hydroxycarboxlic acids which are important as pharmaceuticals and as intermediates for the synthesis of pharmaceuticals.

McMasters, along with Bryker, provides the teaching required to modify the process of Collett. Since all references are drawn to the production of the same ultimate products and specifically teach the necessary elements the expectation for success would be extraordinarily high.

Examiner's Response to Applicants' Arguments Regarding These Rejections

9. Applicant has presented several arguments with regard to these rejections. The Examiner responds to these below:

- a. The Examiner agrees with Applicants' assessment that the water contained in the cyanation reaction is irrelevant.
- b. Applicant further argues that the diasteromeric excess cannot be compared to the enantiomeric excess. This is incorrect. The diastereomeric excess is a direct result of the enantiomeric excess and simply reflects the analytical method (MTPA ester) employed by Effenberger.
- c. Applicant argues that the crucial point of the present invention is to increase the chemical and optical purity. The Examiner agrees and points out that Collett teaches the improvement of optical purity by crystallization explicitly and chemical purity implicitly since that is generally understood to be the object in a recrystallization (See McMasters, page 1, 1st full paragraph).

- d. Applicant argues that there is no suggestion in Collett that the recrystallization can be carried out in the hydrolysis medium. The Examiner agrees and points out that Collett is not relied upon for such suggestion.
- e. Applicant argues that there is no teaching in Collett that the chemical and optical purity of hydroxycarboxylic acids can be improved by a single recrystallization. The Examiner disagrees. Collett clearly teaches (See above) such improvements. Simply because Collett repeats the recrystallization does not imply that the chemical and optical purity of the hydroxycarboxylic acid does not improve with each iteration of the process. The reverse, in fact, is true. Collett produces optically pure (100% ee) material after three recrystallizations.
- f. Finally, Applicant argues in the Supplemental Response in Paper No 7 that water does not increase the solubility of the hydroxycarboxylic acid since it is only slightly soluble in benzene. To this the Examiner responds that to the extent that water is soluble in benzene it increases the solubility of the hydroxycarboxylic acid which is soluble in water (See Bryker, column 5, lines 21-23 for water solubility of mandelic acids).

Applicant's arguments filed 29 April 2002 have been fully considered but they are not persuasive for the reasons indicated above.

Conclusion

10. Claims 11-14 and 16-23 are outstanding. Claims 11-14 and 16-23 are rejected.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul A. Zucker whose telephone number is 703-306-0512. The examiner can normally be reached on Monday-Friday 7:00-3:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Johann R. Richter can be reached on 703-308-4532. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4556 for regular communications and 703-308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Paul A. Zucker
Patent Examiner
Technology Center 1600

August 3, 2002



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